Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

Claim 1 has been amended to recite wherein the first functional unit comprises CCPs 2, 3 and 4 of DAF. Claim 1 has also been amended to recite wherein the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from Fc fragments of IgG4, and a lipid tail. Support for the amendment can be found at least in original claim 4 which has been cancelled by the present amendment.

Claims 1 and 2 have been amended to remove the phrase "encoding a polypeptide" in order to better clarify the metes and bounds of claims 1 and 2.

Claim 2 has been amended to recite the third functional unit is selected from the group consisting of polypeptides derived from Fc fragments of IgG4, and a lipid tail.

Claims 3 and 6 have been cancelled.

Claim 7 has been amended to correct typographical errors and to recite polypeptides derived from Fc fragments of IgG4. Support for this amendment can be found at least in Example 3 and Fig. 11A.

Claim 12 has been amended to recite a protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Claim 14 has been amended to replace the term regulating with inhibiting. Support for this amendment can be found at least at paragraph [0089]. Claim 14 has also been amended to recite administering an effective amount of protein to a mammal, the protein having an amino acid sequence that is at least 95 percent sequence homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23. Support for this amendment can be found at least in original claim 12, Figs. 14, 16, 17, 18A, 18B, and 20.

Claims 16 -18 have been cancelled.

Also by the present amendment, new claims 19 and 20 have been added. Support for new claim 19 and 20 can be found at least Figs. 14, 16, 17, 18A, 18B, and 20.

Below is a discussion of the 35 U.S.C. 112, first paragraph rejections of claims 1-7, 12 and 14-18, the 35 U.S.C. 112, second paragraph rejection of claims 1-2, the 35 U.S.C. §102(b) rejection of claims 1, 3, 4, 14, and 15 and the 35 U.S.C. §103(a) rejection of claims 1, 2, and 4.

1. <u>35 U.S.C. §112 rejection of claims 1-7, 12 and 14-18</u>

Claims 1-7, 12, 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a hybrid DAF-CR1B protein comprising the amino acid sequence selected from the group consisting of SEQ ID NO:13 as shown in Fig. 13 and SEQ ID NO:15 as shown in Figure 9A, (2) a hybrid DAF-IgG4 comprising the amino acid sequence of SEQ ID NO:19, (3) a hybrid

DAF-MCP polypeptide comprising the amino acid sequence of SEQ ID NO:23, and (4) a method of inhibiting classical pathway C3 and C5 convertase mediated or hemolysis comprising the amino acid sequence of SEQ ID NO:13 or SEQ ID NO: 15 for inhibiting classical and alternative C3 convertase, does not reasonably provide enablement for any protein as set forth in claims 1-7, 12 and 16-18 and a method of regulating any complement activity.

The Office Action argues that in view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Claim has been amended to recite that the first functional unit comprises at least CCPs 2, 3 and 4 of DAF. Claim 1 has also been amended to recite that the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from IgG4, and a lipid tail. Applicants respectfully traverse the foregoing rejection as applied to the currently amended claims and submit that the amount of direction or guidance disclosed in the specification is sufficient to enable the skilled artisan to make and use the claimed methods using only routine experimentation.

"[T]o be enabling, the specification ... must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) at 1561 (emphasis added), *quoted in Genentech, Inc. V. Novo Nordisk*

A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. V. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Facts should be considered in determining, whether a specification is enabling include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

Claim 1 as amended recites a protein comprising a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises at least CCPs 2, 3 and 4 of DAF; a first spacer sequence of at least about 200 amino acids, wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, Fc fragments of lgG4, and a lipid tail.

The specification of the present application provides guidance and direction to the skilled artisan commensurate with the scope of the amended claims.

The Office Action argues that in regards to "polypeptides derived from immunoglobulin" other than the Fc fragment of IgG4, there is insufficient guidance as to which amino acids within the full length sequence still maintains receptor binding and effector function.

Claims 1, 2 and 7 have been amended to replace the phrases "polypeptides derived from immunoglobulin" and "polypeptides derived from IgG4" respectively, with the term "Fc fragment of IgG4".

In addition, the specification of the application teaches hybrid complement regulating proteins including functional units comprising CCPs 2, 3 and 4 of DAF (paragraph [0054] of the published application and SEQ ID NO;1), CCPs 8-10 of Complement Receptor 1 (CR1) and CCPs 15-17 of CR1 (paragraph [0056] and SEQ ID NO: 3), as well as functional units that are not derived from complement regulatory proteins including Fc fragments of IgG4 and a lipid tail (paragraph [0064] and Fig. 5). The specification also teaches a first and a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties (paragraph [0060]).

The specification of the application also includes working examples that demonstrate hybrid and chimeric proteins having the amino acid sequences SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23.

Although, the specification of the application does not provide working examples showing proteins having amino acid sequences other than those having

SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23, the specification does provide guidance and direction such that a skilled artisan at the time of the invention would have been able to produce such proteins with an expectation of success without undue experimentation.

For example, the specification teaches expression systems for producing a hybrid protein (paragraphs [0069]-[0074]), as well as methods of production, quantification, and purification of hybrid proteins of the present invention (paragraphs [0075]-[0082]. The specification also teaches assays to determine the functional characterization of proteins of the invention (paragraph [0084]). The specification also teaches ways to demonstrate the *in vivo* therapeutic activity of a hybrid or chimeric protein of the invention (paragraphs [0086]-[0102]).

In addition the specification teaches proteins having amino acid sequences that are at least 95% homologous to those of SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23. The specification teaches that functional units of complement regulating proteins (*e.g.,* DAF, MCP and CR1) and spacers may be altered slightly, particularly at the amino or carboxy terminus and that such alterations occur when a restriction enzyme site is incorporated into the polynucleotide encoding the CCPs or when amino acids are deleted from the N terminus or C terminus of the functional unit (see paragraphs [0054]-[0060]). For example, in one embodiment, a number of amino acids can be deleted from the C terminus of CCP4 of DAF (see Example 1).

Furthermore, the specification teaches that some amino acid substitutions in a sequence may be introduced without affecting the activity of the functional unit as

disclosed in U.S. Pat. No. 6,521,450, which was incorporated by reference in the specification. The specification, therefore, teaches that the functional unit may have less than complete homology to native protein component and that changes may be made by substitution of hydrophilic amino acids for one another, substitution of hydrophobic amino acids for one another and substitution of amino acids of similar mass for one another. The specification also indicates that in other regions of the functional units, especially those unassociated with activity, less subtle changes may be made (see paragraph 0054]).

Accordingly, the specification provides adequate guidance beyond the mere presentation of sequence data to enable one having skill in the art to determine with routine experimentation, positions in the proteins of the present invention as well as the coding sequence thereof, which are tolerant to change and the nature and extent of changes that can be made.

Additionally, claims 1, 2, 5, 7 and 12 are merely directed to a protein comprising a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of DAF; a first spacer sequence of at least about 200 amino acids, wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from Fc fragments of IgG4, and a lipid tail. Applicants' specification provides adequate guidance as to producing such a protein as well as working examples demonstrating a number of such proteins.

Additionally, the Office Action provides no evidence to doubt the veracity of the objective statements made in the specification. It is well established that "[t]he Examiner has the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention" *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A requirement for some experiment does not prevent the satisfaction of the enablement requirement. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1329 (Fed. Cir. 1990). The Federal Circuit has made it clear that "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, *providing sufficient reasons for doubting any assertions* in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1561-1562 (Fed. Cir. 1993). (Emphasis added).

Specifically, the Examiner has not provided any factual evidence to show a reason to doubt the objective truth of the Applicants' statements, which must be relied upon for enabling support; namely, that undue experimentation would have been required to produce the *claimed* protein.

The Office Action argues:

> "Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

> Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495)."

The Applicants fail to see the relevance of these references to showing lack of enablement. The references noted above merely teach well known protein characteristics and provide no mention of the hybrid and chimeric complement inhibiting proteins that are claimed. Moreover, the fact that Stryer et al. and Ngo et al. indicated a change or substitution of one amino acid for another can result in a change in structure/function does not necessarily mean that such changes cannot be made and/or that a skilled artisan could not make such changes to the proteins as claimed.

The Examiner has not established that undue experimentation would have been required to practice the *claimed* protein; specifically, a protein comprising a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises CCPs 2, 3 and 4 of DAF, a first spacer sequence of at least about 200 amino acids, wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, poly peptides derived from Fc fragments of lgG4, and a lipid tail. Therefore, the amount of direction or

guidance disclosed in the specification is sufficient to enable the skilled artisan to make the proteins of claims 1, 2, 5 and 7 using only routine experimentation.

With respect to claim 14, the Office Action argues that there is a lack of *in vivo* working examples for the claimed method of regulating any complement activity in all mammals. As described above, claim 14 has been amended to replace the term regulating with inhibiting. Claim 14 has also been amended to as recite the limitation that the protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

As discussed above, the specification provides adequate support to produce a protein having an amino acid sequence that is at least 95 percent homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23. The specification also teaches assays useful for functional characterization of a protein for use in the method of claim 14, assays for verifying the demonstration of *in vivo* therapeutic activity using proteins of the present invention as well as provides a number of working examples (See paragraphs [0083]-[0102] and Example 1-4).

Accordingly, the specification provides adequate guidance to enable one having skill in the art to produce and administer a complement activity inhibiting protein of the invention as claimed to a mammal using only routine experimentation.

Additionally, Applicant respectively submits that the 35 U.S.C. §112, first paragraph rejection of claims 3, 4, 6, 16, 17, and 18 are rendered moot by the present amendment.

2. 35 U.S.C. §112 rejection of claims 1-7, 12 and 14-18

Claims 1-7, 12, and 14-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant are that the inventor, at the time the application was filed, had possession of the claimed invention.

The Office Action argues that the specification does not reasonably provide a written description of any protein as set forth in claims 1-7, 12, and 16-18 and a method of regulating any complement activity by administering an effective amount of any protein comprising any first functional unit of any complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; any first spacer sequence of at least about 200 amino acids encoding a-polypeptide that does not exhibit complement regulating properties, attached to the first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of polypeptides providing a functional unit of a second complement regulatory protein, polypeptides derived from an immunoglobulin, and polypeptides that enhance binding of the protein to an animal cell to any mammal such as human.

Applicants respectfully traverse this rejection because the specification of the application clearly allows persons of ordinary skill in the art to recognize that Applicants were in possession of proteins as recited in amended claims 1, 2, 5, 7, 12, and 14-15.

Referring to MPEP 2163.02,

> "The fundamental factual inquiry [for determining compliance with the written description requirement] is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing

> date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)."

The specification of the present application describes proteins recited in amended claim 1, 2, 5, 7, 12 and 14-15 by specific examples, amino acid sequences, biochemical and functional characteristics, such that one skilled in the art would recognize that Applicants had possession of the claimed invention.

Claim 1 as amended recites a protein comprising a first functional unit of a first complement regulatory protein, wherein the first functional unit comprises at least CCPs 2, 3 and 4 of DAF; a first spacer sequence of at least about 200 amino acids, wherein the first spacer sequence does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, Fc fragments of IgG4, and a lipid tail.

As discussed above, the specification of the application teaches hybrid complement regulating proteins including functional units comprising CCPs 2, 3 and 4 of DAF (paragraph [0054] of the published application and SEQ ID NO;1), CCPs 8-10 of Complement Receptor 1 (CR1) and CCPs 15-17 of CR1 (paragraph [0056] and SEQ ID NO: 3), as well as functional units that are not derived from complement regulatory proteins including Fc fragments of IgG4 and a lipid tail (paragraph [0064] and Fig. 5). The specification also teaches a first and a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties (paragraph [0060]).

The specification of the application also includes working examples that demonstrate hybrid and chimeric proteins having the amino acid sequences SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23 (Examples 1-4).

Although, the specification of the application does not provide working examples showing proteins having amino acid sequences other than those having SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23, the specification does provide guidance and direction such that the inventors were in possession of the invention recited in amended claim 1 at the time of the invention.

For example, the specification teaches expression systems for producing a hybrid protein (paragraphs [0069]-[0074]), as well as methods of production, quantification, and purification of hybrid proteins of the present invention (paragraphs [0075]-[0082]. The specification also teaches assays to determine and the functional and biochemical characterization of proteins of the invention (paragraph [0082]-[0084]).

In addition the specification teaches proteins having amino acid sequences that are at least 95% homologous to those of SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:19 and SEQ ID NO:23. The specification teaches that functional units of complement regulating proteins (*e.g.,* DAF, MCP and CR1) and spacers may be altered slightly, particularly at the amino or carboxy terminus and that such alterations occur when a restriction enzyme site is incorporated into the polynucleotide encoding the CCPs or when amino acids are deleted from the N terminus or C terminus of the functional unit (see paragraphs [0054]-[0060]). For example, in one embodiment, a number of amino acids can be deleted from the C terminus of CCP4 of DAF (see Example 1).

Furthermore, the specification teaches that some amino acid substitutions in a sequence may be introduced without affecting the activity of the functional unit as disclosed in U.S. Pat. No. 6,521,450, which was incorporated by reference in the specification. The specification teaches that therefore, the functional unit may have less than complete homology to native protein component and that changes may be made by substitution of hydrophilic amino acids for one another, substitution of hydrophobic amino acids for one another and substitution of amino acids of similar mass for one another. The specification also indicates that in other regions of the functional units, especially those unassociated with activity, less subtle changes may be made (see paragraph 0054]).

Accordingly, Applicants have provided specific examples of proteins recited in claim 1, 2, 5, 7, 12 and 14-15 as well as characteristics that can be used to classify and identify such compounds.

Regarding claim 14, the Office Action argues that there is a lack of disclosure as how to regulate any complement activity in all mammals. As described above, claim 14 has been amended to replace the term regulating with inhibiting. Claim 14 has also been amended to recite administering an effective amount of protein to a mammal, the protein having an amino acid sequence that is at least 95 percent sequence homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Similar to the teachings in the specification regarding claim 12 described above, the specification of the present application describes proteins recited in amended claim 14 by specific examples, amino acid sequences, biochemical and functional characteristics, such that one skilled in the art would recognize that Applicants had possession of the protein of claim 14. For example, the specification provides specific guidance regarding amino acid deletion from the N-terminus and C-terminus of the functional units are less important to complement activity inhibition. In addition, the specification also teaches ways to demonstrate the *in vivo* therapeutic activity of a hybrid or chimeric protein recited in claim 14 administered to a mammal (paragraphs [0085]-[0102]).

The Federal Circuit has stated that the written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989) (citations omitted).

As discussed above, the specification clearly allows one skilled in the art to recognize what is claimed based on the disclosure of the characteristics of a protein recited in claim 14, the disclosure of a 4 working examples, as well as means to identify additional proteins for use in the method of claim 14. Therefore, in view of the foregoing, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, they were in possession of the invention, and the invention, in that context, is claimed.

Accordingly, Applicants respectfully request that the 112 first paragraph written description rejection of claims 1, 2, 5, 7, 12 and 14-15 be withdrawn because the specification of the application clearly allows persons of ordinary skill in the art to recognize Applicants were in possession of a protein as recited in claims 1, 2, 5, 7, 12 and 14-15.

Additionally, Applicant respectively submits that the 35 U.S.C. §112, first paragraph rejection of claims 3, 4, 6, 16, 17, and 18 are rendered moot by the present amendment.

3. <u>35 U.S.C. §112 rejection of claims 1-2</u>

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action argues that the term “amino acids encoding” of claims 1 and 2 are indefinite because amino acids do not encode any protein. As discussed above, claims 1 and 2 have been amended to remove the term “amino acids

encoding" and withdrawal of the 35 U.S.C. 112, second paragraph rejection of claims 1-2 are respectfully requested.

The Office Action also argues that the term "substantially" in claims 5, 6, 7, 16, 17, and 18 is indefinite because the metes and bounds of what would constitute a "substantially all" cannot be determined and that the specification nor the claims provide adequate guidance to the interpretation of such a relative term.

The term "substantially" in claims 5 and 7 are definite as the metes and bounds of what would constitute a "substantially all" can indeed be determined and that the specification.

The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co.*, *v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. (See MPEP 2173.05(b))

The term "substantially" is often used in conjunction with another term to describe a particular characteristic of the claimed invention. It is a broad term. *In re Nehrenberg*, 280 F.2d 161, 126 USPQ 383 (CCPA 1960). The court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines contained in the specification.

Here, the term "substantially" is used to modify the terms "all of the amino acids of CCPs 11-14 of CR1" and "all of the amino acids of CCPs 4-7 of CR1 in

claims 5 and "all of the amino acids of CCPs 4-5 of CR1" in claim 7. The specification specifically states:

> "As used herein the term substantially all means that the spacer may lack a few, e.g., 1-10 amino acids from the N terminus and/or the C terminus of the spacer." see [0060]

Therefore, Applicants respectfully put forth that in light of the specification, one of ordinary skill in the art would understand that the phrase substantially all of the amino acids recited in claims 5 and 7 would clearly indicate that a spacer may lack 1-10 amino acids from the N terminus and/or the C terminus of the spacer.

Accordingly, claims 5 and 7 are definite because the metes and bounds of what would constitute a "substantially all of the amino acids" of a CCP in a first or second spacer can be determined because the specification provides adequate guidance to the interpretation of such a relative term and withdrawal of the 35 U.S.C. 112, second paragraph rejection of claims 5 and 7 are respectfully requested.

Additionally, Applicant respectively submits that the 35 U.S.C. §112, second paragraph rejection of claims 6, 16, 17, and 18 are rendered moot by the present amendment.

4. <u>35 U.S.C. §102(b) rejection of claims 1, 3, 4, 14, and 15</u>

Claims 1, 3, 4, 14, and 15 are rejected under 35 U.S.C. 102(b), as being anticipated by the WO95/08570 publication (hereinafter, "the '570 publication").

The Office Action argues that the '570 publication teaches a chimeric fusion protein DAF-MCP, comprising a first functional unit of a first complement regulatory protein such as DAF comprising the short consensus repeats CCPs 2, 3, and 4 of DAF, a first spacer sequence such as a linker ranging from 0-1500 amino acids

attached to said DAF that does not exhibit complement regulatory properties and a second functional unit of a second complement regulatory protein such as CCPs 1-4 of MCP.

Claim 1 as amended is patentable over the '570 publication because the '570 publication does not teach a protein comprising a second functional unit attached to the spacer sequence wherein the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from Fc fragments of IgG4, and a lipid tail.

The '570 publication teaches a chimeric protein having a first functional unit of CCPs 2-4 of DAF and a second functional unit of CCPs 1-4 of MCP and a spacer sequence ranging from 0-1500 amino acids. The '570 publication does not teach a chimeric protein having a second functional unit attached to the spacer sequence wherein the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from Fc fragments of IgG4, and a lipid tail. Therefore, the '570 publication fails to teach all the limitation of claim 1 and withdrawal of the 35 U.S.C. 102(b) rejection of claim 1 is respectfully requested.

Claim 14 is patentable over the '570 publication because the '570 publication does not teach each and every element of the protein recited in claim 14. Amended claim 14 recites in part, administering an effective amount of protein to a mammal, the protein having an amino acid sequence that is at least 95 percent sequence homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

The '570 publication does not teach or suggest in any way administering an effective amount of protein to a mammal, the protein having an amino acid sequence that is at least 95 percent sequence homologous to a protein selected from the group consisting of proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 23.

Therefore, the '570 publication fails to teach all the limitations of claim 14 and withdrawal of the 35 U.S.C. 102(b) rejection of claim 14 is respectfully requested.

Claim 15 depends directly from claim 14 and is allowable because of the reasons set forth above related to claim 14 and because of the limitations recited in claim 14.

Additionally, Applicant respectively submits that the 35 U.S.C. §102(b) rejection of claims 3 and 4 are rendered moot by the present amendment.

5. 35 U.S.C. §103(a) rejection of claims 1, 2 and 4

Claims 1, 2, and 4 are rejected under 35 U.S.C. 103(a), as being unpatentable over WO95/08570 publication (Published March 30, 1995; PTO 892) in view of Harris et al. (J Biol Chemistry 278(38): 36068-36076, September 2003; PTO 892) as evidenced by Smith et al. (J Immunol 154: 2226-2236, 1995: PTO 892).

The Office Action argues that Harris et al. teach a fusion protein comprising a first complementary regulatory protein such as the amino-terminal 1-4 short consensus repeat of DAF fused to human IgG4 Fc domains via a spacer such as 75 amino acids of IGD sequences or MMP cleavage site between the junction of DAF4-IgG4. The Office Action also argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the MCP

functional unit in a fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0-1500 amino acids and MCP as taught in the '570 publication for the Fc domains of human IgG4 taught by Harris et al.

Claim 1 has been amended to recite a protein comprising a second functional unit attached to the spacer sequence wherein the second functional unit is selected from the group consisting of CCPs 8-10 of Complement Receptor 1 (CR1), CCPs 15-17 of CR1, polypeptides derived from Fc fragments of IgG4, and a lipid tail.

Claim 1 is not obvious in view of is the '570 publication in view of Harris et al. as evidenced by Smith et al. because Harris et al. teaches away from linking a DAF functional unit to the Fc domains of human IgG4 using the spacer sequence of the '570 publication.

The '570 publication teaches a chimeric protein having a first functional unit of CCPs 2-4 of DAF and a second functional unit of CCPs 1-4 of MCP. The '570 patent does not teach a chimeric protein having a second functional unit attached to the spacer sequence wherein the second functional unit is comprised of polypeptides derived from IgG4.

Harris et al. teach fusion protein prodrugs comprising four human DAF short consensus repeats linked to IgG4 Fc. However, Harris et al. teach that the fusion protein prodrugs have a markedly decreased complement inhibitory activity when compared with the parent regulator *in vitro* (Abstract). Due to the stated inhibitory activity, Harris et al. teach that DAF and IgG4 Fc must be linked by a 75 amino acid sequence of the Interglobular Domain (IGD) of aggrecan which contains specific cleavage sites for metalloproteinases and/or aggrecanases (Fig. 2B, p. 36069, left

col. and p. 36070, right col.) Harris et al. indicates that the cleavage sites allow for cleavage of the IgG4 functional unit of the prodrug from DAF, in order to release the active complement regulator (Abstract). Smith et al. merely discuss that the Fc region of IgG4 normally is devoid of complement activity.

According to the teachings Harris et al., a DAF-IgG4 fusion protein that does not include a cleavable linker would retain the IgG4 Fc functional unit and would have markedly decreased complement inhibitory activity when compared with the parent regulator (e.g., DAF) *in vitro*. Thus, Harris et al. teaches away from the use of a spacer amino acid sequence that does not include specific cleavage sites allowing for the release of the active complement regulator in a DAF-IgG4 Fc fusion protein spacer sequence in order to avoid decreased complement inhibitory activity.

The spacer sequence of the '570 publication does not include specific cleavage sites allowing for the release of the active complement regulator. Therefore, a combination of the '570 publication and Harris et al. would teach that a simple substitution of IgG4 Fc for MCP in the fusion protein of the '570 publication would have a markedly decreased complement inhibitory activity when compared with the parent regulator. Therefore, one skilled in the relevant art would not look to combine the spacer sequence and DAF functional unit of the '570 publication with the IgG4 Fc functional unit of Harris et al. because Harris et al. teaches away from such a combination. Accordingly, it would not have been obvious to one of ordinary skill in the art at the time of the invention to link a DAF functional unit to the Fc domains of human IgG4 using the spacer sequence of the '570 publication because Harris et al. teach away from such a combination.

Claim 2 depends directly from claim 1 and is allowable because of the aforementioned deficiencies in the rejection with respect to claim 1. In addition, Claim 2 is not obvious in view of the '570 publication and Harris et al. as evidenced by Smith et al. because: (1) the combination of the '570 publication, and Harris et al. do not teach or suggest a third functional unit attached to a second spacer, wherein the third functional unit is selected from the group consisting of polypeptides derived from IgG4, and a lipid tail; and (2) Harris et al. teaches away from linking a complement regulatory protein to the Fc domains of human IgG4 using the spacer sequence of the '570 publication.

The Office Action argues that claim 2 differs from the '570 publication only in that the recited protein further comprises a third functional unit attached to the second functional unit by a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties. The Office Action further argues that it would be obvious to one of ordinary skill in the art at the time the invention was made to fuse the fusion protein of the '570 publication to the human IgG4 Fc via a long spacer of Harris to form a fusion protein comprising CCPs 1-4 of DAF, a first spacer ranging from 0-1500 amino acids, CCPs 1-4 of MCP, a second spacer ranging from 0-1500 amino acids and the Fc domains of IgG4.

As discussed above, the '570 publication teaches a chimeric protein having a first functional unit of CCPs 2-4 of DAF and a second functional unit of CCPs 1-4 of MCP and a spacer sequence ranging from 0-1500 amino acids. The '570 publication does not teach a third functional unit attached to a second spacer, wherein the third

functional unit is selected from the group consisting of polypeptides derived from IgG4, and a lipid tail.

Harris et al. teach fusion protein prodrugs comprising four human DAF short consensus repeats linked to IgG4 Fc and Smith et al. merely discuss that the Fc region of IgG4 normally is devoid of complement activity. Harris et al. as evidenced by Smith do not teach a third functional unit attached to a second spacer, wherein the third functional unit is selected from the group consisting of polypeptides derived from IgG4, and a lipid tail.

To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Moreover, the Office Action has failed to include any discussion or provide any teaching showing that it was desirable to include a third functional unit attached to a second spacer, wherein the third functional unit is selected from the group consisting of polypeptides derived from IgG4, and a lipid tail. Without such a teaching or suggestion, the '570 publication in view of Harris et al. as evidenced by Smith et al. fail to teach all of the limitations of the claimed invention and withdrawal of the rejection of claim 2 is specifically requested.

Furthermore, Harris et al. teaches away from linking a complement regulatory protein to the Fc domains of human IgG4 using the spacer sequence of the '570 publication. The Federal Circuit has stated that teaching away is the antithesis of art suggesting that the person of ordinary skill go in the claimed direction (*In re Fine,* 837 F.2d 1071, 5 USPQ2d 1596 (Fed Cir. 1988).

According to the teachings Harris et al., a complement regulatory protein(Creg) and IgG4 fusion protein (Creg-IgG4) that does not include a cleavable linker would retain the IgG4 Fc functional unit and would have markedly decreased complement inhibitory activity when compared with the parent regulator (*e.g.,* Creg-Creg-IgG4) *in vitro*. Thus, Harris et al. teaches away from the use of a spacer amino acid sequence that does not include specific cleavage sites allowing for the release of the active complement regulators in a Creg-Creg-IgG4 Fc fusion protein in order to avoid decreased complement inhibitory activity.

The spacer sequence of the '570 publication does not include specific cleavage sites allowing for the release of the active complement regulators. Therefore, a combination of the '570 publication and Harris et al. would teach that a Creg-Creg-IgG4 Fc fusion protein of would have a markedly decreased complement inhibitory activity when compared with the parent regulator (*e.g.,* Creg-Creg). Therefore, one skilled in the relevant art would not look to combine the spacer sequence and any number of Creg functional units of the '570 publication (DAF and/or MCP) with the IgG4 Fc functional unit of Harris et al. because Harris et al. teaches away from such a combination.

Accordingly, it would not have been obvious to one of ordinary skill in the art at the time of the invention to link two Creg functional units to the Fc domains of human IgG4 using the spacer sequence of the '570 publication because the combination of the '570 publication, and Harris et al. do not teach or suggest a third functional unit attached to a second spacer, wherein the third functional unit is selected from the group consisting of polypeptides derived from IgG4 and Harris et

al. teaches away from linking a complement regulatory protein to the Fc domains of human IgG4 using the spacer sequence of the '570 publication.

Additionally, Applicant respectively submits that the 35 U.S.C. §103(a) rejection of claim 4 is rendered moot by the present amendment.

In view of the foregoing, it is respectfully submitted that the present application is in a condition of allowance and allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this matter to our Deposit Account No. 20-0090.

Respectfully submitted,

/Richard A. Sutkus/
Richard A. Sutkus
Reg. No. 43,941

TAROLLI, SUNDHEIM, COVELL,
& TUMMINO L.L.P.
1300 East Ninth Street, Suite 1700
Cleveland, Ohio 44114
Phone:(216) 621-2234
Fax: (216) 621-4072
Customer No.: 68,705